

National TIA/Ischemic Stroke Project
Annotated Clinical Bibliography
Revised November 2000

Stroke Prevention and Management

Acute interventions: American Heart Association Conference Proceedings. *Stroke* 1997;28:1518-21.

Hyperacute administration of rt-PA was identified as the most important advance in controlling and preventing medical and neurological complications of acute ischemic stroke. NINDS study results indicated that IV rt-PA significantly improved stroke outcomes at three months when following protocol requirements. Other new and emerging treatments for acute ischemic stroke include the use of antithrombotic and antiplatelet aggregating drugs, neuroprotectants (i.e., calcium entry antagonists, glutamate antagonists, sodium channel and glycine antagonists, opioid antagonists and antioxidant-free radical scavengers), and intracranial angiography and carotid stenting. Among others, the following issues were identified as areas of future focus: patient behavior and recruitment, prehospital/hospital care, diagnostics, availability of trained physicians, outcome measures, time to treatment, charges/reimbursement, public policy and education.

Adams HP et al. Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association Medical/Scientific Statement 1994; *Circulation* Sept 1994;90(3):1588-1601.

The goal of this report was to provide information about the current management of acute ischemic stroke and recommendations for the initial care (within the first 24 hours of stroke) based on data from the clinical trials. No recommendations about rehabilitation or chronic medical or surgical measures to prevent stroke were made. The discussion begins with suggestions for increasing public awareness and training EMS personnel in rapid recognition of stroke signs and symptoms. In addition to the usual emergency steps used to stabilize a patient, recommended emergent evaluative tests for stroke include a computerized axial tomography (CT) scan of the head, EKG, chest x-ray and cardiac monitoring. Cautious use of oral antihypertensives is suggested for patients who are markedly hypertensive. Early mobilization and measures to prevent the subacute complications of stroke (aspiration, malnutrition, pneumonia, DVT, decubitus ulcers, contractures and joint abnormalities) were strongly recommended. At the time, thrombolytic therapy was not recommended but the authors acknowledged that pilot studies were promising. A subsequent addendum was published regarding thrombolytic use.

Albers GW et al. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the ad hoc committee on guidelines for the management of transient ischemic attacks, Stroke Council, American Heart Association. *Stroke* 1999;30:2502-11.

The approach to stroke prevention among patients who have already had their first TIA includes identification and modification of stroke risk factors. Modifiable stroke risk factors include hypertension, cardiac disease (particularly atrial fibrillation), diabetes, hypercholesterolemia, cigarette smoking, excessive use of alcohol and physical inactivity. Antiplatelet agents are typically the treatment of choice for prevention of future stroke in patients who have experienced a TIA of presumed atherothrombotic origin. Adjusted-dose oral anticoagulation with warfarin continues to be the therapy of choice for stroke prevention in patients with atrial fibrillation (AF) who have had a TIA. Surgical management may include carotid endarterectomy (CEA), transluminal angioplasty with placement of stents, extracranial-intracranial bypass and surgery for occlusive disease of the vertebrobasilar system.

Alberts MJ. Diagnosis and treatment of ischemic stroke. *Am J Med* Feb 1999;106:211-21.

An up-to-date review on diagnosis and treatment of stroke, summarizing many studies published during the 1990s. The focus of these studies included the areas of rapid recognition of stroke, appropriate diagnostics, treatment of acute stroke (including prevention of complications, reversal of acute stroke effects and prevention of subsequent strokes) and the role of the primary care physician.

Brott T and Bogousslavsky J. Treatment of acute ischemic stroke. *N Engl J Med* Sep 7, 2000;343(10):710-22.

This article reviews data from clinical trials and current treatment options for patients with acute ischemic stroke. Topics included in this discussion include pathophysiology and targets for intervention, early evaluation and supportive treatment, intravenous thrombolytic therapy, intra-arterial thrombolytic therapy, antithrombotic and antiplatelet drugs, neuroprotection, treatment in the hospital, integrated stroke-intervention teams and stroke units and rehabilitation.

Bruno A. Ischemic stroke, part 1: early, accurate diagnosis. *Geriatrics* March 1993;48(3):26-34.

A review of the standard for treatment of acute stroke. Emphasizes the importance of avoidance of emergent blood pressure reduction, blood glucose control, reduction of cerebral edema and appropriate use of anticoagulation, especially in patients with AF. Reviews the need for measures to minimize future strokes, such as diabetes control, blood pressure management, long-term anticoagulation in selected patients and proper use of CEA.

Helgason CM, Wolf PA. American Heart Association Prevention Conference IV: Prevention and rehabilitation of stroke: executive summary. *Circulation* Jul 15, 1997;96(2):701-07.

This summary reports on the state of knowledge on stroke epidemiology, etiologic basis, treatment and rehabilitation. Recommendations include;

1) enhancing support for screening and follow-up programs for hypertension and other modifiable stroke risk factors, particularly targeting high-risk populations; 2) intensifying efforts to prevent cigarette smoking and encouraging smoking cessation through elimination of advertising, economic disincentives, public education and other measures; and 3) encouraging substantial increases in funding of clinical stroke research appropriate to the major public health burden of this condition.

Hemphill JC 3rd. Ischemic stroke: clinical strategies based on mechanisms and risk factors. *Geriatrics* Mar 2000;55(3):42, 47-48, 51-52.

Current approaches to ischemic stroke prevention and treatment emphasize a tailored approach to each stroke patient based on stroke localization and risk factors, rather than a one size fits all approach. Many preventive and treatment strategies are under investigation and will undoubtedly further refine stroke therapy in the future. This article contains four case studies and includes a discussion on treatment strategies following each of the scenarios. Tables included in this article identify criteria for IV t-PA for treatment of acute ischemic stroke and stroke risk reduction in symptomatic carotid artery stenosis and AF.

Ingall TJ. Preventing ischemic stroke. Current approaches to primary and secondary prevention. *Postgrad Med* May 15, 2000;107(6):34-36, 39-42, 47-50.

Since few patients are eligible to receive intravenous tissue plasminogen activator (tPA), the only approved treatment for acute stroke, prevention is the most important treatment strategy to reduce the burden of the disease. The major strategies for secondary stroke prevention are: 1) appropriate evaluation to identify the mechanism of the initial stroke; 2) CEA for patients with symptomatic carotid artery stenosis of 50 percent or more; 3) oral anticoagulation with warfarin for patients with nonvalvular AF; and 4) use of various antiplatelet agents (including aspirin (ASA), ticlopidine, clopidogrel, and the combination of ASA and slow-release dipyridamole). Whether treatment of risk factors reduces the risk of secondary stroke is currently being evaluated in clinical trials.

Matchar DB et al. Medical treatment for stroke prevention. *Ann of Int Med* July 1, 1994;121(1):54-55.

Review of 33 clinical trials on the use of anticoagulation or antiplatelet therapy in the prevention of stroke. It points out that warfarin is effective in patients with AF, but also results in more complications. ASA is less effective but safer. In patients with TIA or minor stroke, antiplatelet therapy reduces the risk of future stroke.

McCorry DC and Matchar DB. Stroke prevention: the emerging strategies. *Hosp Prac* March 15, 1996;123-34.

A pragmatic discussion of various stroke prevention strategies including warfarin for AF, antithrombotic therapy for TIA/stroke and CEA. Potential barriers to the use of warfarin (e.g., bleeding complications, sensitivity, inconvenience of follow-up monitoring, and drug interactions)

are addressed. Establishing anticoagulation clinics is suggested as a potential remedy to some of these barriers.

McGuire JR, Harvey RL. The prevention and management of complications after stroke. *Phys Med & Rehab Clinics of N Amer* Nov 1999;4(10):857-75.

Current evidence suggests that careful monitoring and prevention of medical complications during stroke recovery can have a positive impact on outcome. Patients with acute stroke are at risk to develop thromboembolic complications when they are in a "prethrombotic state." This state can be defined as a physiological status in which an individual has an activated coagulation system poised to generate intravascular thrombus. The elderly are especially at risk for this condition. Although certain markers can be measured to indicate the presence of this state, mobility is the best clinical marker of risk for DVT. Patients who walk 50 feet daily, with or without an assistive device, are at low risk for venous thromboembolism.

National Stroke Association *Stroke: The First Six Hours. Emergency Evaluation and Treatment* 1993;ISSN;3-12.

The National Stroke Association (NSA) prepared this consensus statement to focus on early recognition and expedient medical management of "brain attacks". Using a six hour therapeutic window, emphasis is placed on the issues of patient responsibility (e.g., recognition of stroke symptoms and immediate activation of the EMS), transport services (e.g., speed, safety, support), initial management (e.g., history, examination, labs), diagnostic testing (e.g., CT, MRI arteriography, ultrasound) and clinical intervention (e.g., surgical or medical management). Citing current findings that stroke treatments are most effective when they are applied as soon as possible, the NSA recommends that patients be directed to hospitals that are prepared to provide immediate diagnostic testing and treatment.

Pushpangadan M et al. Evidence-based guidelines for early stroke management. *Hosp Med* 1999;60:105-14.

After a review of literature regarding stroke management, the authors produced a series of substantiated guidelines to assist the admitting doctor in the optimal management of early stroke care.

Sacco RL et al. Risk factors and their management for stroke prevention: outlook for 1999 and beyond. *Neurology* 1999;53(7 Suppl 4):S15-24.

Hypertension, including borderline hypertension, is probably the most important stroke risk factor based on degree of risk and prevalence. However, cardiac morbidity, cigarette smoking, diabetes, physical inactivity, and high levels of alcohol consumption are also strongly related to stroke risk. High levels of blood cholesterol and homocysteine may also increase stroke risk. Mortality after stroke is highest within the first 30 days but remains elevated to a degree that depends on the presenting stroke syndrome, stroke subtype, and other co-morbidities. The

risk for recurrence is highest within 30 days after a first stroke (depending on the type of infarct), history of hypertension, and blood glucose levels on admission. Predictors of late recurrence include cardiac disease, hypertension, and heavy alcohol use. Only about half of stroke survivors are independent six months after a stroke, and quality of life is decreased. Understanding factors that predispose to stroke and determine its outcome will help in the design of acute stroke trials and in prevention programs.

Wolf PA et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack. A statement for healthcare professionals from the stroke council of the American Heart Association. *Stroke* 1999;30:1991-94.

There are three treatment strategies to prevent recurrent stroke in patients with TIA or mild ischemic stroke. For patients with AF, dose-adjusted warfarin sodium is administered unless there is a specific contraindication for that medication. In the presence of contraindications, the patient should be treated with ASA 50 to 325 milligrams per day. The treatment of choice for moderate to severe carotid artery stenosis is CEA by a surgeon with a low complication rate. In the absence of AF or carotid artery stenosis, treatment with a daily dose of 50 to 325 milligrams of ASA is of demonstrated benefit. Therapeutic decisions based on the best available evidence need to be incorporated into routine clinical practice, and the impact of treatments on patient outcomes should be systematically monitored. Dissemination of preventive guidelines lags behind clinical trial and consensus statement results. Overall, healthcare organizations need to develop systems that ensure that patients at high risk for stroke are identified, screened, and treated appropriately.

Antithrombotic Therapy for Stroke Prevention

Adams HP et al. Studies of Org 10172 in patients with acute ischemic stroke. *Haemostasis* 1992;22:99-103.

A report of data from pilot studies of Org 10172, a low-molecular weight heparinoid, in patients with acute ischemic stroke. The goals of these pilot studies were to determine the potential safety, establish a potentially optimal dose and regimen and provide some evidence of efficacy of Org 10172. The studies were divided into two phases. Phase I was a dose escalation study which tested five escalating doses of Org 10172. In Phase II, a larger number of patients were given the drug, at the potentially desirable dose, to provide additional information about safety and possible efficacy. These pilot studies led to the funding of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) to test the hypothesis that Org 10172 is superior to placebo in improving the likelihood of a favorable outcome at three months after stroke for 1300 patients with ischemic stroke.

Albers GW and Tijssen JGP. Antiplatelet therapy: new foundations for optimal treatment decisions. *Neurology* 1999;53(7 Suppl 4):S25-31.

Individuals with ischemic cerebral events due to atherothrombosis should typically receive antiplatelet agents. ASA is the best-studied antiplatelet agent and has been used in stroke prevention for many years. Trials evaluating ASA have, over time, enrolled more patients and tested lower ASA doses. No individual trial conducted in cerebrovascular patients has established the optimal ASA dose for prevention of vascular events, but meta-analyses of trials at different dose ranges and the two single trials that directly compared different doses strongly suggest that the benefit of ASA is independent of dose. On the basis of large clinical trials versus ASA, three other antiplatelet agents (ticlopidine, clopidogrel, and the combination of ASA plus extended-release dipyridamole) have all been shown to be effective for stroke prevention. Physician opinions regarding the efficacy of these agents in indirect comparisons and the differences in their safety profiles, availability, and cost will influence the choice of agent for the individual patient.

Albers GW. Role of ticlopidine for prevention of stroke. *Stroke* June 1992;23(6):912-16.

This comment was written following publication of two large randomized trials which demonstrated that ticlopidine can decrease the risk of stroke. The Canadian-American Ticlopidine Study (CATS) randomized 1053 patients to ticlopidine or placebo therapy and found that primary outcome events occurred in 10.8% per year of ticlopidine patients versus 15.3% per year in the placebo group. The Ticlopidine-Aspirin Stroke Study (TASS) randomized 3069 patients to treatment with ticlopidine or ASA in a double-blind study design and reported a 21% risk reduction rate for 3-year fatal or nonfatal stroke. Ticlopidine efficacy and current favorable risk/benefit ratio data support ticlopidine use, particularly for patients who are unable to take ASA.

Anderson DC et al. Preliminary report of the stroke prevention in atrial fibrillation study. *New Eng J of Med* March 22, 1990;322(12):863-68.

This study was designed to test the safety and efficacy of warfarin and ASA separately in the primary prevention of ischemic stroke and systemic thromboembolism in patients with AF unrelated to rheumatic valvular disease. Using two groups (total of 1244 patients) in this randomized clinical trial, the following results were calculated in November 1989 after following the patients for a mean of 1.13 years:

- *primary events in group 1 = 1.6 percent per year of 393 patients in the warfarin and ASA treatment arms with 8.3 percent per year in the 195 patients in the placebo arms*
- *in all 517 patients given ASA, primary events occurred 3.2 percent per year versus 6.3 percent per year in the 528 patients given a placebo.*

Bennett CL et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* Jun 15, 2000;342(24):1773-77.

The estimated incidence of ticlopidine-associated thrombotic thrombocytopenic purpura is one per 1,600 to 5,000 patients treated, whereas no clopidogrel-associated cases have been observed among 20,000 closely monitored patients treated in Phase 3 clinical trials and cohort studies. Because of the association between ticlopidine use and thrombotic thrombocytopenic purpura and other adverse effects, clopidogrel has largely replaced ticlopidine in clinical practice. There have been clinical and laboratory findings reported on 11 patients who developed thrombotic thrombocytopenic purpura during or soon after treatment with clopidogrel. Ten of the 11 patients received clopidogrel for 14 days or less before the onset of thrombotic thrombocytopenic purpura. Although ten of the 11 patients had a response to plasma exchange, two required 20 or more exchanges before clinical improvement occurred and two had relapses while not receiving clopidogrel. One patient died despite undergoing plasma exchange soon after diagnosis. Thrombotic thrombocytopenic purpura can occur after the initiation of clopidogrel therapy, often within the first two weeks of treatment. Physicians should be aware of the possibility of this syndrome when initiating clopidogrel treatment.

Berge E et al. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. *Lancet* April 8, 2000;355:1205-10.

The Heparin in Acute Embolic Stroke Trial (HAEST) was a multicenter, randomized, double-blind trial to test the effect of low-molecular-weight (LMW) heparin or ASA for the treatment of 449 patients with acute ischemic stroke and AF. The primary goal was to test whether treatment with LMW heparin, started within 30 hours of stroke onset, is superior to ASA for the prevention of recurrent stroke during the first 14 days. The frequency of recurrent ischemic stroke during the first 14 days was 19/244 (8.5 percent) in LMW heparin-allocated patients versus 17/225 (7.5 percent) in ASA-allocated patients. There were no significant differences in functional outcome or death at 14 days, or three months. The present data do not provide any evidence that LMW heparin is superior to ASA for the treatment of acute ischemic stroke in patients with AF.

Bhatt DL. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. *Am Heart J* 2000;140(1):67-73.

In a more recent examination of data from the CAPRIE trial, the effect of clopidogrel on the high rate of ischemic events (i.e., angina, TIA, severe limb ischemia) leading to hospitalization for patients with atherosclerotic disease was examined. Hospitalization related to hemorrhage was also studied. Compared with ASA, clopidogrel also resulted in a 7.9 percent relative risk reduction in a combined end point of vascular death, stroke, myocardial infarction or rehospitalization for ischemic events or bleeding (15.1percent to 13.7 percent). The authors concluded that treatment with

clopidogrel results in a significant decrease in the need for rehospitalization for ischemic events or bleeding when compared with ASA (1,502 compared to 1,673, $p=.010$).

Diener HC et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* Nov 1996;143(1-2):1-13.

This randomized, placebo-controlled, double-blind trial was designed to investigate the safety and efficacy of low-dose ASA, modified-release dipyridamole, and the two agents in combination for the secondary prevention of ischemic stroke. Data from 6,602 patients were analyzed. Patients with prior stroke or transient ischemic attack (TIA) were randomized to treatment with ASA alone (50 mg daily), modified-release dipyridamole alone (400 mg daily), ASA and dipyridamole in a combined formulation, or placebo. Stroke risk in comparison to placebo was reduced by 18 percent with ASA alone, 16 percent with dipyridamole alone and 37 percent with combination therapy. Risk of stroke or death was reduced by 13 percent with ASA alone, 15 percent with dipyridamole alone and 24 percent with the combination. Headache was the most common adverse event, occurring more frequently in dipyridamole-treated patients. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received ASA in comparison to placebo or dipyridamole. The authors concluded that: 1) ASA 25 mg twice daily and dipyridamole, in a modified-release form, at a dose of 200 mg twice daily have each been shown to be equally effective for the secondary prevention of ischemic stroke and TIA; 2) when co-prescribed the protective effects are additive, the combination being significantly more effective than either agent prescribed singly; and 3) low-dose ASA does not eliminate the propensity for induced bleeding.

Easton JD et al. Antiplatelet therapy: views from the experts. *Neurology* 1999; 53(7 Suppl 4):S32-37.

ASA was the first antiplatelet agent to be used for stroke prevention and is still the most frequently prescribed preventive treatment for ischemic stroke. However, because the results of clinical studies with ASA have been inconsistent, the dose of ASA required for stroke prevention in persons with cerebrovascular disease has been a subject of debate among stroke neurologists. Despite the controversy, ASA is now recognized as the treatment standard against which other antiplatelet agents are compared. Although other antiplatelet agents has been directly compared with ASA in a large, randomized clinical trial, the lack of direct comparisons among these alternative antiplatelet therapies complicates decisions regarding long-term care of patients with cerebrovascular disease.

The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* Nov 29, 1990;323(22):1505-11.

Unblinded, randomized, controlled trial of long-term, low-dose warfarin therapy in patients with nonrheumatic AF involving 420 patients followed for an average of 2.2 years. The control group was not given warfarin but could choose to take ASA. Conclusions: long-term low-dose warfarin therapy is highly effective in preventing stroke in patients with non-rheumatic AF, and can be quite safe with careful monitoring.

The CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel vs. aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* Nov 16, 1996;348:1329-39.

This is a randomized, blinded study comparing clopidogrel to ASA for reducing stroke, AMI or vascular death. The patients had known clinical vascular disease, including histories of strokes and AMI. Clopidogrel reduced the risk of the combined outcome by 8.7 percent compared to the ASA group. There were no major differences in safety. There were reversible, minor side effects in a very small percentage of patients treated with clopidogrel.

Connolly SJ et al. Canadian atrial fibrillation anticoagulation (CAFA) study. *J Am Coll Cardio.* Aug 1991;18(2):349-55.

A randomized, double blind, placebo controlled trial to assess if warfarin can reduce systemic embolization and its inherent risk of hemorrhage. One hundred and eighty-seven patients were allocated to warfarin and 191 to placebo. The combined end point was incidence of stroke, systemic embolization and fatal or intracranial hemorrhage. The endpoint occurred in 3.5 percent of warfarin-treated patients and 5.2 percent of placebo-treated patients. Fatal or major hemorrhage occurred in 2.5 percent of the warfarin group and 0.5 percent of the placebo group. As a result of the publication of two other "positive" studies of similar design and objective, this study was stopped early before completion of its planned recruitment of patients. Conclusions: The estimate of benefit of anticoagulant therapy in AF (relative risk reduction of 37 percent) was consistent with estimates from previous reports and supported the use of warfarin in patients with nonrheumatic valvular AF.

European Atrial Fibrillation Trial Study Group: optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Eng J Med* 1995;333(1):5-10.

This is the post hoc analysis of the EAFT study. It looked at hemorrhagic events in patients with AF on warfarin, reviewing the course of 214 patients. Events were lowest in patients with INRs between 2.0 and 3.9. Most major bleeds were associated with INRs > 5.0.

Ezekowitz MD et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Eng J Med* Nov 12 1992;327(20):1406-12.

Randomized, double-blind, placebo-controlled study to evaluate low-intensity warfarin treatment in 571 patients with nonrheumatic AF. The end-point of the warfarin arm was an INR of 1.2 – 1.5. The reduction in risk with warfarin therapy was 79 percent. The incidence of bleeding complications was low in both groups and not significantly different. Conclusions: low-intensity anticoagulation with warfarin prevented cerebral infarction in patients with nonrheumatic AF without producing an excess risk of major hemorrhage. The benefit extended to patients over 70 years of age.

Gent M et al. The Canadian/American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* June 3, 1989;1215-20.

A randomized, blinded study comparing placebo to ticlopidine in patients with recent thromboembolic stroke. The end-point was recurrent stroke, AMI or vascular death. The relative risk reduction was 30 percent in the ticlopidine group. Side effects of ticlopidine were rare and were reversible.

Gubitz G et al. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Sys Rev* 2000;2:CD000029.

The aim of this review is to assess the net result of antiplatelet therapy in acute ischemic stroke. Randomised trials comparing antiplatelet therapy started within 14 days of the stroke with control in patients with definite or presumed ischaemic stroke were reviewed and eight trials involving 41,325 patients were included. Two trials testing ASA 160 to 300 milligrams once daily started within 48 hours of onset contributed 98 percent of the data. Antiplatelet therapy was associated with a small but definite excess of two symptomatic intracranial hemorrhages for every 1,000 patients treated, but this was more than offset by a reduction of seven recurrent ischemic strokes for every 1,000 patients treated. Antiplatelet therapy with ASA 160 to 300 milligrams daily and started within 48 hours of onset of presumed ischemic stroke reduces the risk of early recurrent ischemic stroke without a major risk of early hemorrhagic complications and improves long-term outcome.

Jiang He et al. Aspirin and risk of hemorrhagic stroke: meta-analysis of randomized controlled trials. *JAMA* Dec 9, 1998;280(22):1930-35.

Data from 16 trials with 55,462 participants and 108 hemorrhagic strokes were analyzed. The mean dosage of ASA was 273 mg/d and the mean duration of treatment was 37 months. ASA use was associated with an absolute risk reduction in myocardial infarction of 137 events per 10,000 persons and in ischemic stroke, a reduction of 39 events per 10,000 persons. ASA treatment was also associated with an absolute risk increase in hemorrhagic stroke of 12 events per 10,000 persons. This risk did not differ by participant or study design characteristics.

Kahn JK. Anticoagulant therapy for atrial fibrillation. *Postgrad Med* Sept 1, 1992;92(3):119-30.
A review of four major clinical trials of anticoagulation for AF. It concludes that patients with AF should be treated with warfarin, especially if high risk for embolism is present. The authors also concluded that patients with contraindications to warfarin and paroxysmal AF should receive ASA.

Larrue V et al. Hemorrhage transformation in acute ischemic stroke: potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke* May 1997;28(5):957-60.

This was a post-hoc analysis of the European Cooperative Acute Stroke Study (ECASS) II. The authors examined the outcome of intracranial hemorrhage in both the placebo and treatment arms. Severity of neurological deficit and the presence of early ischemic changes on CT scan were identified as being associated with increased risk for cerebral hemorrhage. Other factors were increasing age and the use of t-PA.

Petersen P et al. Placebo controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* Jan 28, 1989;175-79.

A randomized trial in patients with AF comparing warfarin, ASA and placebo. The primary endpoint was thromboembolic complications and the secondary endpoint was death. Warfarin reduced the incidence of the primary endpoint compared to ASA and placebo, which did not differ significantly. The incidence of bleeding was much higher in the warfarin group, although none of the hemorrhages was fatal.

SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* Nov 30, 1991;338(8779):1345-49.

This placebo-controlled clinical trial was designed to study the efficacy of 75 mg ASA daily in preventing stroke and death after a TIA or minor stroke. Of the 1360 patients in the study, 676 were randomly assigned to ASA treatment and 684 to placebo treatment. Compared to the placebo group, results for the ASA group showed an 18 percent reduction in the risk of primary outcome events (stroke or death) and reductions of 16-20 percent in the risk of secondary outcome events (stroke; stroke or two or more TIAs within one week of each other necessitating a change of treatment; or myocardial infarction). The lower dose ASA regimen did not reduce the risk of hemorrhagic side effects when compared with higher dose ASA therapy. Features of ASA therapy that merit further study include the beneficial effect of long-term ASA therapy, ASA in adjunct therapy and ASA efficacy in the acute phase.

Sherman DG. Aspirin, ticlopidine and warfarin: when and why. *J of Stroke and Cerebrovascular Diseases* 1997;6(4):178-79.

A review of the literature related to the use of ASA, ticlopidine and warfarin in stroke prevention. The 1994 report of the Antiplatelet Trialists' Collaboration reported that antiplatelet therapy reduces

nonfatal vascular events and stroke by approximately 25 percent. The Ticlopidine-Aspirin Stroke Study results showed a statistically significant reduction in stroke when ticlopidine use was compared to ASA or placebo. However, several issues to be considered when ticlopidine therapy is being considered include potential adverse effects (i.e., gastrointestinal intolerance, rash, increase in total serum cholesterol, neutropenia), efficacy of long-term therapy, risk of vascular events and cautious consideration of subgroup analyses, many of which lacked statistical power. When clopidogrel (an agent chemically related to ticlopidine) was studied and compared to ASA, a relative risk reduction of 8.7 percent was reported for ischemic stroke, myocardial infarction and peripheral disease. Safety and risk of neutropenia were the same for the clopidogrel and ASA groups. The best documented benefit of warfarin is for stroke prevention in AF and cardiogenic embolism. Issues related to anticoagulation include risk for hemorrhage, hypertension, history of bleeding and intensity of anticoagulation.

Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study: final results. *Circulation* August 1991;84(2):527-39.

Double blind, multicenter, randomized trial that compared ASA or warfarin with placebo and involved 1330 inpatients and outpatients followed for 1.3 years. Primary events or death were reduced by 58 percent by warfarin and 32 percent by ASA. The risk of significant bleeding was 1.5, 1.4 and 1.6 percent per year in patients assigned to warfarin, ASA and placebo, respectively. Conclusions: ASA and warfarin are both effective in reducing ischemic stroke and systemic embolism in patients with AF. Because warfarin-eligible patients composed a subset of all ASA-eligible patients, the magnitude of reduction in events by warfarin versus ASA cannot be compared. Too few events occurred in warfarin-eligible patients to directly assess the relative benefit of ASA compared to warfarin, and the trial is continuing to address this issue. Patients with nonrheumatic AF who can safely take either ASA or warfarin should receive prophylactic antithrombotic therapy to reduce the risk of stroke.

Tanahashi N et al. Ticlopidine improves the enhanced erythrocyte aggregability in patients with cerebral infarction. *Stroke* Jul 1993;24(7);1083-86.

This study examined the ability of ticlopidine to reduce platelet aggregation in stroke patients in the chronic phase post-stroke. Erythrocyte aggregation rates were significantly lowered in the 14 patients studied, as were hematocrits and fibrinogen levels.

UK-TIA Study Group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J of Neur, Neurosurg and Psych*; 1991; 54:1044-54.

A randomized, blinded study comparing ASA in doses of 300 mg and 1200 mg daily to placebo in patients with TIA or minor strokes. Both ASA arms yielded similar results which were a 15 percent reduction in the risk of major stroke, AMI or vascular death.

Rapid-acting Antihypertensives

Broderick J et al. Blood pressure during the first minutes of focal cerebral ischemia. *Ann of Emer Med* Sept 1993; 22(9):96-101

This study was developed as part of a multicenter pilot study of recombinant plasminogen activator in acute stroke. The study included 69 patients from 13 hospitals in three metropolitan communities with acute ischemic stroke. It was designed to determine if blood pressure declines spontaneously during the first few minutes and hours of focal cerebral ischemia. Blood pressures were recorded at the first contact with the patient, on arrival at the hospital, during pretreatment evaluation, immediately prior to treatment and at spaced intervals over the first 24 hours. For purposes of analysis, patients who received antihypertensives during the first several hours after stroke onset were excluded and only blood pressures during the first four hours following symptom onset were analyzed. The patients were divided into three groups based on their initial systolic blood pressure: upper quartile (n=17, 171-240 mmHg); lower quartile (n=20, 100-130 mmHg) and middle two quartiles (n=32, 131-170 mmHg). It was observed that elevated systolic and diastolic blood pressures spontaneously decreased in more than 80 percent of the cases. The findings of this study further support that changes in blood pressure during the first hours after stroke are related to initial blood pressure measurements and that mildly or moderately elevated blood pressure in ischemic stroke patients usually does not require urgent pharmacologic intervention.

Goldstein LB. Should antihypertensive therapies be given to patients with acute ischemic stroke? *Drug Safety* Jan 2000;22(1):13-18.

The management of hypertension in the setting of acute ischemic stroke remains a source of confusion and controversy. Lowering blood pressure in this situation may be hazardous because of impaired cerebral autoregulation. Treatment may be considered in patients who are otherwise candidates for thrombolytic therapy, have severe hypertension or specific concomitant medical conditions (including acute myocardial infarction, aortic dissection, hypertensive encephalopathy, or severe left ventricular failure). A precipitous decline in blood pressure such as is often seen with sublingual calcium antagonists should be avoided. Drugs with the capacity to dilate cerebral vessels should be used with caution as they have the potential to increase intracranial pressure. The potential for certain classes of drugs to impair the recovery process should be considered when choosing an antihypertensive for treatment of these patients.

Grossman E et al. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* October 23/30, 1996;276(16):1328-30.

The use of sublingual nifedipine in hypertensive emergencies and pseudoemergencies was once a common practice in a variety of settings

despite a lack of outcome data to assess safety and efficacy of this intervention. At least nine reports were published from 1994 through 1996 with findings of serious adverse effects (i.e., aphasia, hemiparesis, loss of consciousness, myocardial infarction etc.) when sublingual or oral nifedipine was administered. Available data suggests that the absorption of nifedipine from the buccal mucosa is poor and that sublingual administration results in inconsistent delivery. Following a lengthy review of data regarding the safety and efficacy of sublingual nifedipine for hypertensive emergencies, the Cardiorenal Advisory Committee of the Food and Drug Administration concluded that the practice of administering sublingual nifedipine should be abandoned due to safety and efficacy issues.

Messerli FH, Kowey P and Grodzicki T. Sublingual nifedipine for hypertensive emergencies. *Lancet* (Letters to the Editor) Oct 5, 1991;338:881

In October 1991, this response to a July editorial recommending sublingual nifedipine for hypertensive emergencies was published. In an effort to urge physicians to refrain from following this recommendation, the authors cite published studies verifying that decreases in arterial blood pressure after administration of sublingual nifedipine are unpredictable and difficult to reverse. Two additional studies found dramatic decreases in systolic blood pressure to potentially be problematic, particularly in hypertensive emergencies associated with acute myocardial infarction or cerebrovascular accident. A final reference to the deliberation and decision of the cardiorenal advisory committee of the U.S. Food and Drug Administration further supports the restraint of administering sublingual nifedipine in medical emergencies based on lack of dose-response information or risk assessment of complications.

Stason WB et al. Safety of nifedipine in patients with hypertension: a meta-analysis. *Hypertension* Jul 1997;30(1):7-13.

A review of the published studies on the use of nifedipine in hypertension focusing on adverse events. There were no differences in adverse events in patients treated with nifedipine compared to other antihypertensives. Most of the studies looked at the use of sustained-release or extended-release forms of the drug, and support its use in appropriate patients.

CT/MRI

American Heart Association Medical/Scientific Statement. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke. *Stroke* May 1997;28:1480-97.

These guidelines were developed to educate clinicians on the use of diagnostic imaging in patients with acute stroke or at high risk for stroke. In patients with TIAs, computed tomography (CT) of the head may detect cerebral infarction or exclude other lesions that may simulate stroke. It is recommended that the initial evaluation of a patient with stroke include a noncontrast CT scan of the head. CT results can document or exclude

intracerebral hemorrhage (near 100 percent sensitivity) and subarachnoid hemorrhage (96 percent sensitivity). Magnetic resonance imaging (MRI) studies are more expensive, more time-consuming and less available than CT studies. However, they are more capable of detecting acute and small infarcts and are superior to CT for imaging vessels. Magnetic resonance angiography (MRA) is a generic term applied to a variety of approaches to vascular imaging by MRI. Advantages of using MRI include its usefulness in identifying posterior circulation strokes and small hemorrhages. It can also date hemorrhages when indicated and is more sensitive than CT (90 percent) for detection of ischemic infarction within the first 24 hours of stroke onset.

Barber PA et al. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. (Alberta Stroke Programme Early CT Score). *Lancet* May 13, 2000;355(9216):1670-74.

A total of 203 consecutive patients with ischemic stroke were treated with intravenous alteplase within 3 hours of symptom onset in two North American teaching hospitals. All pretreatment CT scans were prospectively scored. The score divides the middle-cerebral-artery territory into ten regions of interest. Primary outcomes were symptomatic intracerebral hemorrhage and 3-month functional outcome. Ischemic changes on the baseline CT were seen in 117 (75 percent) of 156 treated patients with anterior-circulation ischemia included in the analysis (23 had ischemia in the posterior circulation and 24 were treated outside the protocol). Baseline ASPECTS value correlated inversely with the severity of stroke on the National Institutes of Health Stroke Scale. This CT score is simple and reliable and identifies stroke patients unlikely to make an independent recovery regardless of treatment with thrombolytics.

Kidwell CS et al. Diffusion MRI in patients with transient ischemic attacks. *Stroke* June 1999;30:1174-80.

Although the value of diffusion MRI has been established for patients with ischemic stroke, it has not been systematically investigated in patients with TIA. A conventional and diffusion MRI was obtained on 42 consecutive patients with symptoms of TIA and imaging data was compared with a contemporaneous group of 23 completed stroke patients. A total of 20 of the 42 (48 percent) patients demonstrated focal abnormalities on diffusion-weighted imaging (DWI). When present, DWI signal changes in TIA patients were less pronounced and smaller in volume than those in completed stroke patients. TIA symptom duration was significantly longer for DWI-positive than for DWI-negative patients, 7.3 versus 3.2 hours. Diffusion MRI demonstrates ischemic abnormalities in nearly half of clinically define TIA patients. In nearly half, the diffusion MRI changes may be fully reversible, while in the remainder the diffusion MRI finding herald the development of a parenchymal infarct despite transient clinical symptoms.

Lansberg MG et al. Advantages of adding diffusion-weighted magnetic resonance imaging to conventional magnetic resonance imaging for evaluating acute stroke. *Arch Neurol* Sep 2000;57(9):1311-16.

This prospective cohort study was designed to determine the yield of adding diffusion-weighted magnetic resonance imaging (DWI) to a conventional MRI protocol for acute stroke. A total of 52 patients with a clinical diagnosis of acute stroke that presented within 48 hours after symptom onset were included. Conventional MRI correctly identified at least one acute lesion in 71 percent (34/48) to 80 percent (39/49) of patients who had an acute stroke. With the addition of DWI, this percentage increased to 94 percent (46/49). The observers' confidence with which lesions were rated as acute and the lesion conspicuity was significantly higher for DWI than for conventional MRI. During the first 48 hours after symptom onset, the addition of DWI to conventional MRI improves the accuracy of identifying acute ischemic brain lesions in patients who experienced a stroke.

Rosenwasser RH, Armonda RA. Diagnostic imaging for stroke. *Clin Neurosurg* 2000;46:237-60.

A highly technical article which describes the various diagnostic imaging techniques for acute stroke in great detail. Discussion, examples of scans and commentary are all focused on accurate, rapid delivery of thrombolytic therapy.

Thrombolytic Therapy

Albers GW et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) Study. *JAMA* Mar 1, 2000;283(9):1145-50

This prospective, multicenter study of 389 consecutive patients enrolled between February 1997 and December 1998 at 57 medical centers in the United States was designed to assess the safety profile and to document clinical outcomes and adverse events in patients treated with intravenous tPA for acute stroke in clinical practice. Median time from stroke onset to treatment was two hours 44 minutes, and the median baseline National Institutes of Health Stroke Scale score was 13. The 30-day mortality rate was 13 percent. At 30 days after treatment, 35 percent of patients had very favorable outcomes and 43 percent were functionally independent. Thirteen patients (3.3 percent) experienced symptomatic intracerebral hemorrhage, including seven deaths. Twenty-eight patients (8.2 percent) had asymptomatic intracerebral hemorrhage within three days of treatment with tPA. Protocol violations were reported for 127 patients (32.6 percent), and included treatment with tPA more than three hours after symptom onset in 13.4 percent, treatment with anticoagulants within 24 hours of tPA administration in 9.3 percent, and tPA administration despite systolic blood pressure exceeding 185 mm Hg in 6.7 percent. This study, conducted at multiple institutions throughout the United States,

suggests that favorable clinical outcomes and low rates of symptomatic intracerebral hemorrhage can be achieved using tPA for stroke treatment.

American Heart Association, Medical/Scientific Statement. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. *Circulation* 1996;94:1167-74. (Also published in *Stroke* 1996;27:1711-18.)

Based on the data of five clinical trials of intravenously administered thrombolytic drugs, this publication supplements the 1994 American Heart Association (AHA) Stroke Council guidelines for physicians who care for persons within the first few hours after stroke symptom onset. The recommendations address timing, treatment risks, patient assessment, dosing, thrombolytic selection, diagnostics prior to administration, contraindications and management of bleeding complications.

Buchan AM et al. Effectiveness of tPA in acute ischemic stroke: outcome relates to appropriateness. *Neurology* Feb 8, 2000;54(3):679-84.

This study was designed to examine whether the demonstrated efficacy of tPA for acute ischemic stroke can be effective in a community setting. A total of 68 consecutive patients with acute ischemic stroke treated with IV tPA within three hours of symptom onset by attending general neurologists in a busy teaching hospital were included in this study. Of these patients, 26 (46 percent) made a full recovery and 38 (67 percent) regained independence. The 11 patients who violated protocol had a lower probability of independence and full neurologic recovery and a higher probability of symptomatic hemorrhage and death compared with those of the 57 patients treated according to NINDS guidelines. The risk of symptomatic hemorrhage is similar to that noted in randomized trials. Treating patients who violate protocol exposes them to excess risk with no observable benefit.

Clark WM, Wissman S, Albers G, Jhanamdas J, Madden K., Hamilton S et al. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study. *JAMA* 1999;282:2019-26.

In June 1996, the Food and Drug Administration approved the use of intravenous recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke within three hours of symptom onset. This randomized study was designed to test the efficacy and safety of rt-PA in the same group of people during a timeframe of three to five hours after symptom onset. The results of 547 patients (rt-PA = 272 and placebo = 275) identified no significant treatment benefit for rt-PA given during the extended timeframe in the early recover, 30-day or 90day timeframes. Therefore, use of intravenous rt-PA for stroke beyond three hours after symptom onset is not recommended.

Cornu C et al. Thrombolysis in acute stroke pooling project: a meta-analysis on individual patient data. *J Clin Neurosci* Jan 1999;6(1):20-23.

The objectives of this ongoing study are to assess the efficacy of thrombolysis to reduce death or severe disability, to identify predictors of

death and hemorrhagic transformation and to identify subgroups with a better response to treatment. This project will assist in efforts to define subpopulations that are more likely to benefit from this treatment (which cannot be achieved using tabulated data) and designing future trials.

Fagan SC, Morgenstern LB, Petitta A et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology* 1998;50:883-90.

This is a post-hoc analysis of the original NINDs study examining the cost-effectiveness of tPA treatment. It used Markov model comparing 1000 theoretically treated patients with 1000 untreated patients. Hospitalization costs would have been \$1.7 million higher, rehabilitation costs \$1.4 million lower and nursing home costs \$4.8 million lower in the treated group. The long-term outcome was 564 QALYs saved in the treated group.

Frank JI. Contemporary acute ischemic stroke therapy with intravenous recombinant tissue plasminogen activator. *Clin Neurosurg* 2000;261-66.

In spite of heightened medical and lay interest in acute ischemic stroke treatment, the utilization of intravenous rt-PA to treat eligible patients has been slow to gain acceptance in the treatment arena. This might be due, in part, to the mixed results of the European Cooperative Acute Stroke Studies and the NINDS and Stroke rt-PA trial. The results of these studies not only offer information regarding rt-PA use to treat acute ischemic stroke, they have also brought attention to the opportunity for improvement that exists in emergency triage and treatment systems. The University of South Alabama Stroke Center and University of Texas monitored acute ischemic stroke management data for one year periods. Their findings indicate that the use of rt-PA for patients with acute ischemic stroke might increase with the improvement of public awareness regarding stroke symptoms and the critical role of emergent evaluation and treatment. Regarding rt-PA exclusions that are independent of time of presentation, it is important to continue investigating other promising stroke treatments and strengthening inter-disciplinary partnerships to improve current stroke management processes.

Frankel MR et al. Predicting prognosis after stroke. A placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurol* 2000;55:952-59.

Data from the placebo arms of parts one and two of the NINDS rt-PA Stroke Trial were used to identify variables that could predict a poor outcome (moderately severe disability, severe disability, or death three months after stroke). Data collected at baseline (study entry), two hours after study entry and 24 hours and seven to ten days after stroke were used to determine the likelihood of a poor outcome at three months. The primary purpose of this study was to develop models that can be used by clinicians to predict which patients with acute ischemic stroke might be at high risk for severe disability or death in the absence of thrombolytic therapy. Although this study did not have the statistical power to provide a clear answer, rt-PA-treated patients with baseline findings identified as

predictive of poor prognosis in the placebo group were less likely to have a poor outcome.

Furlan A, Higashida R, Weschler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark W, Silver F, Rivera F et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study. *JAMA* 1999;282:2003-11.

Based on the results of the first Prolyse in Acute Cerebral Thromboembolism (PROACT1) trial, this multicenter, randomized trial investigated the clinical efficacy and safety of intra-arterial (IA) recombinant prourokinase (r-proUK) in patients with acute ischemic stroke less than 6 hours after symptom onset caused by middle cerebral artery (MCA) occlusion. It is noted that the increased frequency of early symptomatic intracranial hemorrhage found in this study is difficult to compare with results of previous IV thrombolysis trials because the sites of arterial occlusion and recanalization rates were not identified in the earlier studies. When compared with 59 patients who received heparin only, the 121 patients who received 9 mg of IA r-proUK plus heparin a median of 5.3 hours after symptom onset were 58% more likely to have slight or no neurological disability at 90 days.

Hacke W, Kaste M, Fieschi C. et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA* Oct 4, 1995;274(13):1017-25.

This is another tPA study published several months before the NINDs study. It was flawed by a high drop-out rate in the treatment arm. When analyzed by intention to treat, tPA showed no benefit in the primary outcomes (clinical status) at 90 days. Several secondary analyses showed some benefit for the tPA arm and the hospital stay was shorter in the tPA arm.

Hacke W, Kaste M, Fieschi C et al. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke from the European-Australian Acute Stroke Study Investigators (ECASS II); *Lancet* Oct 17, 1998;352:1245-51.

This was a second study by the authors of the previous study designed to correct the flaws identified in the first study. tPA again showed no benefit for the primary outcome. Of note is the fact that both studies admitted patients up to six hours following symptom onset, compared to three hours in the NINDs study.

Hacke W et al. Thrombolysis in acute ischemic stroke: controlled trials and clinical experience. *Neurology* 1999;53(7 Suppl 4):S3-14.

This article contains a general discussion of the use of thrombolysis for ischemic stroke. Approval of rt-PA was granted after large, randomized, placebo-controlled studies by the NINDS and ECASS I and II showed significant improvement in three-month outcomes with rtPA despite a significant risk for symptomatic hemorrhage. A combined analysis of the three studies shows mortality and morbidity to be significantly reduced. The most substantial treatment barrier is the narrow time window, which may be expanded if long-term experience shows that this is possible. Most

stroke patients arrive at the hospital too late to be eligible for screening and treatment. The authors conclude that education of the public and physicians may help to overcome this difficulty.

Katzan IL et al. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA* Mar 1, 2000;283(9):1151-58.

The objective of this study was to assess the rate of intravenous tPA use, the incidence of symptomatic intracerebral hemorrhage (ICH), and in-hospital patient outcomes throughout 29 hospitals in the Cleveland, Ohio, metropolitan area from July 1997 through June 1998. A total of 3,948 patients were admitted with a primary diagnosis of ischemic stroke to a study hospital. A total of 70 patients (1.8 percent) admitted with ischemic stroke received tPA. Of those 70 patients, 11 (15.7 percent) had a symptomatic intracranial hemorrhage (six were fatal) and 35 (50 percent) had deviations from national treatment guidelines. In-hospital mortality was significantly higher among patients treated with tPA (15.7 percent) compared with patients not receiving tPA (5.1 percent). The Cleveland community experience with tPA for acute ischemic stroke may differ from that reported in clinical trials.

Kwiatkowski TG et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med* Jun 10, 1999;340(23):1781-87.

In the NINDS Trial, a total of 624 patients with stroke were randomly assigned to receive either tPA or placebo. Outcome data were collected over a period of 12 months after the occurrence of stroke. The primary outcome measure was a "favorable outcome," defined as minimal or no disability as measured by the Barthel index, the modified Rankin Scale and the Glasgow Outcome Scale. The patients treated with tPA were at least 30 percent more likely to have minimal or no disability at 12 months than were the placebo-treated patients, but there was no significant difference in mortality at 12 months between the two groups. These results indicate a sustained benefit of tPA for such patients.

Mohr JP. Thrombolytic therapy for ischemic stroke from clinical trials to clinical practice. *JAMA* Mar 1, 2000;283(9):1189-91.

This article is a commentary on two articles (Albers and Katzan) contained in the same edition of this journal. The nihilistic attitude toward treatment of acute ischemic stroke is a thing of the past, and much of the progress is directly attributable to innovative, high-quality clinical trials. The important studies by Albers et al and Katzan et al provide equally compelling lessons and much need cautions regarding extending thrombolytic therapy for stroke to routine clinical practice. It is only with careful patient selection, individualized therapy according to the causative lesion, strict adherence to treatment guidelines, and evidence-based therapeutic decision making and drug administration by physicians with

experience using these new agents and interventions that patients will derive optimal benefit from hyperacute treatment of stroke.

NINDs Study Group. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Eng J Med* Dec 14, 1995;333(24):1581-87.

This was the first study to show the efficacy of tPA in acute stroke patients. The drug was administered within three hours of symptom onset. In Part I of the study, the outcomes measured were neurologic deficit at 24 hours and in Part II, the clinical outcome at three months was measured. There were no differences between the placebo and tPA arm at 24 hours, but the tPA group had significant improvement in the test measures at three months compared to placebo. tPA treated patients were 30 percent more likely to have minimal or no deficit at three months compared to placebo. Symptomatic cerebral hemorrhage was found in 6.4 percent of the treated patients in the tPA arm and in 0.6 percent in the placebo arm.

NINDs Study Group. Generalized efficacy of tPA for acute stroke: subgroup analysis of the NINDs tPA Stroke Trial. *Stroke* Nov 1997;28(11):2119-25.

*This is another post-hoc analysis from the original NINDs trial looking at clinical and laboratory findings to see if subgroups could be identified that were more likely to benefit from tPA therapy. For this effort, 624 cases (312 tPA, 312 placebo) from the two NINDS trials were randomized and 27 baseline variables were identified. These variables were used to construct a multivariate model of favorable outcomes that was assessed using the global test for multiple outcomes published in *Stroke*, 1996. The results did not identify a correlation between any pretreatment information from the clinical work-up and the patient's response to tPA. Subselection of patients based on pretreatment information was not supported by this post analysis.*

NINDs tPA Study Group. Intracerebral hemorrhage after intravenous tPA therapy for ischemic stroke. *Stroke* Nov 1997;28(11):2109-18.

This double-blind, placebo-controlled trial studied baseline and post treatment variables associated with symptomatic and asymptomatic intracerebral hemorrhage in a multi-center randomized study of tPA for acute ischemic stroke. The absolute increase in the risk of symptomatic intracerebral hemorrhage was low for all tPA –treated patients but increased in the presence of a severe neurological deficit and clear sign of brain edema or mass effect on pretreatment CT scan. Treatment with tPA was more likely to result in an excellent neurological outcome at three months in both subgroups of patients with a higher risk of symptomatic intracerebral hemorrhage than treatment with placebo.

Part 7: The era of reperfusion: Section 2: Acute Stroke. *Circulation* Aug 22 2000;102 Suppl(8):I204-I216.

Early treatment of stroke depends strongly on recognition of the event by the patient, family members, or bystanders. Rapid activation of the EMS system is essential to optimize care of the patient with stroke. Key points in the management of stroke can be remembered by using the mnemonic of the 7 D's: Detection, Dispatch, Delivery, Door, Data, Decision and Drug. Delay may occur at any point so the response at each point must be skilled and efficient. This article includes an algorithm for suspected strokes, the National Institute of Health Stroke Scale (NIHSS) and a listing of the contraindications to tPA therapy for acute stroke. Also included are tables that identify the presenting clinical features of hemorrhagic and nonhemorrhagic stroke, the general management of acute stroke, NINDS-recommended stroke evaluation targets for potential fibrinolytic candidates and suggested antihypertensive therapy for patients with acute stroke. This article is an excellent resource for education of general practitioners on the treatment of stroke.

Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN). Practice Advisory: Thrombolytic therapy for acute ischemic stroke summary statement. *Neurology* 1996;47:835-39.

The Quality Standards Subcommittee mission is to develop scientifically sound, clinically relevant practice parameters for the practice of neurology. This AAN practice advisory is a summary based on a background paper developed by the AHA Stroke Council. A panel selected by the AAN and working in conjunction with the AHA Stroke Council reviewed the relevant literature. Recommendations for initiating thrombolytic treatment, the management of bleeding complications, antithrombotic and antiplatelet aggregating drugs and the use of thrombolytic drugs are included.

Schmulling S et al. One-year follow-up in acute stroke patients treated with rtPA in clinical routine. *Stroke* Jul 2000;31(7):1552-54.

A recent placebo-controlled study provided evidence of a sustained benefit at one-year from systemic thrombolysis in patients with acute ischemic stroke. The scope of this study was to determine whether comparable results may be attained in everyday practice if current management guidelines are closely met. Between March 1996 and July 1998, 150 consecutive patients with acute ischemic stroke were treated with systemic thrombolysis using alteplase in accordance with the AHA guidelines. The patients were followed up for 12 months after treatment. Baseline characteristics and complication rates were comparable to those of the NINDS study. The overall rate of recurrent stroke was 6.6 percent and the TIA rate 3.3 percent at one-year. Six patients (4 percent) died after the first three months, none of them due to recurrent stroke, and five had already been severely disabled at three months. These observations

further encourage the routine use of rtPA for the treatment of acute ischemic stroke in strict accordance with the AHA guidelines.

Tanne D et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. *Stroke* Feb 2000;31(2):370-75.

Few data exist on the use of tPA in very elderly patients. Hospitals within several selected cities with an organized stroke triage system and experience with the use of intravenous tPA for acute ischemic stroke per published protocols, were retrospectively surveyed. This study was based on retrospective record review and examined the characteristics, complications and short-term outcome of acute ischemic stroke patients aged ≥ 80 years treated with tPA. Risk of intracerebral hemorrhage was 7 percent in the elderly age group. Elderly patients were more likely to be treated by stroke specialists (87 percent), less likely to have an identified protocol deviation (13 percent) and were discharged more often to nursing care facilities (17 percent). No evidence for withholding tPA treatment for acute ischemic stroke in appropriately selected patients aged ≥ 80 years was identified.

Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2000;(2):CD000213.

The objective of this review was to assess the safety and efficacy of thrombolytic agents in patients with acute ischemic stroke. Seventeen trials including 5,216 patients were included. Fifteen trials were double-blinded. Two trials used intra-arterial administration but the rest used the intravenous route. About 50 percent of the data come from trials testing intravenous tPA. Thrombolytic therapy significantly increased the odds of death within the first ten days. Despite this, thrombolytic therapy, administered up to six hours after ischemic stroke, reduced the proportion of patients who were dead or dependent at the end of follow-up. Trials testing intravenous recombinant tPA suggest that it may be associated with slightly less hazard and more benefit when given up to six hours after stroke. Further trials will be needed to identify which patients are most likely to benefit from treatment and the environment in which it may best be given, before thrombolytic therapy should be adopted on a wider scale.

DVT Prophylaxis

Anderson FA et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151:933-38.

This report describes the findings of a community-wide study of venous thromboembolism conducted in 16 short-stay general hospitals in the Worcester, Massachusetts metropolitan area. The study population constituted all patients discharged during an 18-month period with a diagnosis of acute deep vein thrombosis (DVT) and/or pulmonary embolism. There were a total of 151,349 acute-care discharges from the

participating hospitals, and 1,372 (0.9 percent) had a discharge diagnosis of acute DVT and/or pulmonary embolism. Of 405 patients with a first-recognized episode of venous thromboembolism, 47 (12 percent) died in the hospital. Pulmonary embolism was listed on the death certificate as a contributing cause of death in 20 (43 percent) of those 47 patients. The case-fatality rates for DVT and pulmonary embolism were five percent and 23 percent, respectively.

Clagett GB et al. Prevention of venous thromboembolism. *Chest* Oct 1992;102(4):391S-407S.

Stroke patients with a paretic or paralyzed lower extremity are at increased risk of DVT. Pooled results of three previous studies (one in 1977 and two in 1987) showed that the incidence of DVT in these patients when untreated was 47 percent. Data from these studies and one additional 1991 study showed a 45 percent reduction of relative risk with low-dose heparin (LDH) therapy and a 79 percent reduction of relative risk with low-molecular weight (LMW) heparin therapy. According to a 1989 study, intermittent pneumatic compression devices have been beneficial in neurosurgical patients. Because many of these patients have hemiparesis, this intervention should also benefit stroke patients. These five studies support the use of LDH, LMW heparin or an IPC device for prevention of venous thromboembolism in patients with ischemic stroke.

Muir KW et al. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *QJM* Jun 2000;93(6):359-64.

This randomized, controlled trial, with blinded data review occurred in a University hospital acute stroke unit. A total of 98 patients were allocated to graded compression stockings or to standard care alone. DVT incidence was determined at baseline and at day 7 by color-flow Doppler ultrasound. One patient developed a clinically manifested DVT, while none of the patients developed pulmonary thromboembolism. DVT was detected in seven out of 65 patients allocated to graded compression stockings, while DVT involving femoral veins was detected in 3 out of 65 patients. In the first week after stroke, radiologically detected DVT remains common, but is usually clinically silent. Graded compression stockings produced a reduction in DVT incidence comparable to that in other patient groups, but the reduction was not statistically significant, and the magnitude of effect size requires confirmation.

Turpie AGG. Prophylaxis of venous thromboembolism in stroke patients. *Seminars in Thrombosis and Hemostasis* 1997;23(2):155-57.

Estimates of the frequency of DVT in untreated patients range from 20 to 75 percent. This wide range reported depends on the methods used to detect DVT and on the degree of lower limb paralysis. Pulmonary embolism is the third most common cause of death in stroke patients and occurs in 1-2 percent of patients who do not receive prophylactic treatment. Each study in which the primary objective was to evaluate thrombosis prophylaxis with heparin showed a significant risk reduction in venous thrombosis without clinically important bleeding. In one study,

low-dose heparin reduced the frequency of DVT from 12 of 16 patients (75 percent) to two of 16 patients (13 percent). Evidence is accumulating that low-molecular-weight heparin is more effective and safer than standard heparin in patients at high risk for thrombosis and with major hemostatic challenges. The major limitation of the prophylaxis studies in ischemic stroke is the small sample size in each.

Changing Clinical Processes

Alberts MJ, Dawson DV, Massey EW. A follow-up survey of clinical practices for the use of heparin, warfarin, and aspirin. *Neurology* Apr 1994;44(4):618-21.

This was a physician survey comparing 1986 practices with 1993 practices. In the treatment of acute stroke, the use of anticoagulation was decreased in the later survey as was the intensity of treatment.

Alberts MJ et al. Acute stroke teams: results of a national survey. National Acute Stroke Team Group. *Stroke* 1998 Nov;29(11):2318-20.

The formation of acute stroke teams is one approach that can be used to accelerate the delivery of acute stroke care. A survey of major stroke program directors and neurovascular experts throughout the United States was conducted. This survey focused on issues related to the presence of acute stroke team, their staffing, operational features, and utilization at the surveyed programs and hospitals. Out of 45 centers, 91 percent of the respondents indicated that they currently had an acute stroke team, 66 percent of these were developed between 1995 and 1997. Staffing of acute stroke teams consisted of attending physicians (95 percent), nurses or study coordinators (73 percent), fellows (49percent) and residents (46percent). In almost all cases (98 percent), the acute stroke team was led by a neurologist or neurosurgeon, and 98 percent of the acute stroke teams operated on a 24-hours-per-day, 7-days-per-week basis. The use of acute stroke teams may assist in providing more rapid medical care to stroke patients and increase the use of some acute therapies. Extension of the acute stroke team concept to nonacademic hospitals appears feasible.

Alberts MJ et al. Recommendations for the establishment of primary stroke centers. *JAMA* Jun 21 2000;283(23):3102-09.

This review was conducted to develop recommendations for the establishment and operation of primary stroke centers as an approach to improve the medical care of patients with stroke. Key elements of primary stroke centers include acute stroke teams, stroke units, written care protocols, and an integrated emergency response system. Important support services include availability and interpretation of computed tomography scans 24 hours every day and rapid laboratory testing. The establishment of primary stroke centers has the potential to improve the care of patients with stroke.

Anderson DC. How Twin Cities neurologists treat ischemic stroke: policies and trends. *Arch Neuro* Oct 1993;50(10):1098-103.

A survey of physicians conducted first in 1988 and again in 1991 after definitive clinical trials on the efficacy of CEA were published. Almost all physicians favored CEA in good risk patients before and after the publication of the trials. The percentage favoring CEA in older, sicker and symptomatic patients increased between 1988 to 1991, from 67 percent to 92 percent. Fewer physicians favored evaluation of bruit patients (33 percent vs. 24 percent).

Barnett HJ and Buchan AM. The imperative to develop dedicated stroke centers. *JAMA* Jun 21, 2000;283(23):3125-56.

This article is a commentary on the importance of developing stroke units. Leaders in stroke care, whether neurologists or dedicated and knowledgeable internists or geriatricians, must take the initiative in organizing and launching new regional dedicated stroke units, the core of the stroke center. The personnel in emergency medical services must be made aware of the urgency of stroke and of the location of the units and centers.

Bonnono C et al. Acute ischemic stroke emergi-path. *J Emerg Nurs* Aug 2000;26(4):340-42.

To facilitate the management of stroke patients, an Oregon Health Sciences University (OHSU) multidisciplinary team developed a suspected acute stroke Emergi-path and clinical guidelines for drug administration (included in the article). The stroke Emergi-path provides step-by-step guidelines for the early care of this high-risk population. This tool was designed to facilitate rapid evaluation of patients with stroke symptoms to direct interventions.

Collins D. An acute stroke service: potential to improve patient outcome without increasing length of stay. *Ir Med J* May 2000;93(3):84-86.

This article presents a three-year audit of the first acute stroke service in an Irish teaching hospital, which was carried out prospectively on 193 patients admitted to the acute stroke service from July 1996 to the end of June 1999. In years one, two and three, respectively, a reduction in mortality (from 19 percent to 15 percent to nine percent) was observed. Likewise, an increasing percentage of patients discharged home were noted (from 55 percent to 64 percent to 68 percent). This study confirms the value of organized stroke care to patients in reduction in mortality and morbidity without increasing length of stay or disability. The authors suggest that every acute hospital should have an organized stroke care unit.

Goldstein LB et al. North Carolina stroke prevention and treatment facilities survey. Statewide availability of programs and services. *Stroke* Jan 2000;31:66-70.

Because a number of randomized controlled trials indicate that organization of care may effect outcomes after stroke, this study was completed to determine the statewide availability of stroke prevention and

treatment programs and to identify underserved regions in North Carolina. Several categories of data were collected from North Carolina's 125 inpatient care facilities via a one-page survey. Some of the data categories included diagnostic studies (i.e., CT, MRI, etc.), stroke services (i.e., tPA protocol, neurologist on staff, etc.), and programs' organization features (i.e., stroke care map, organized stroke team, etc.). Based on their responses, individual hospitals were categorized as providing less than full basic, full basic or advanced stroke services. Of North Carolina's 100 counties, 84 had \geq one inpatient care facilities. Overall, 97 percent of the state's population resided in counties with a medical facility providing some level of stroke prevention or treatment services. Hospitals with full basic or advanced services were available to 52 percent of the population. Identifying the availability of stroke services is a first step in improving the level of stroke care and increasing its usage within geographic regions.

Hill MD et al. Building a "brain attack" team to administer thrombolytic therapy for acute ischemic stroke. *CMAJ* May 30, 2000;162(11):1589-93.

This article discusses the organization of acute stroke care at one hospital in Calgary, Canada involving a multidisciplinary team that included the stroke team, the department of neurology, the department of diagnostic imaging, the department of emergency medicine, the stroke unit and emergency medical services (EMS). The composition of the stroke team and key processes are described. Other aspects of this effort include: a public education campaign about the symptoms of stroke; training for paramedics regarding a quick stroke assessment examination to identify patients who might be candidates for thrombolytic therapy; and, emergency department staff trained to triage stroke as a life-threatening emergency. After three years, their efforts have resulted in improved patient outcomes, shorter time from symptom onset to treatment and acceptable adverse event rates. Areas for continued improvement include the door-to-needle time and broader education of the public about the symptoms of acute ischemic stroke.

Indredavik B et al. Stroke unit treatment: 10-year follow-up. *Stroke* Aug 1999;30(8):1524-27.

The aim of the present trial was to examine the effects of stroke unit care after ten years of follow-up. This study follows the same 110 patients with symptoms and signs of an acute stroke who were allocated to the stroke unit and 110 patients to a general ward. The outcome after ten years was measured by the proportion of patients at home, the proportion of patients in an institution, the mortality and the functional state of patients as assessed by the Barthel Index. After ten years, 21 (19.1 percent) of the patients randomized to the stroke unit and nine (8.2 percent) of the patients randomized to the general ward were at home. A total of 83 (75.5 percent) of the patients from the stroke unit and 96 (87.3 percent) of the patients from the general ward had died and six (5.4 percent) and five (4.5 percent), respectively, were in an institution (e.g., nursing home; NS).

This study shows that stroke unit care improves survival and functional state and increases the proportion of patients able to live at home up to ten years after their stroke.

Kalra L et al. Alternative strategies for stroke care: a prospective randomised controlled trial. *Lancet* Sept 11, 2000;356:894-99,869-70.

A single-blind, randomized, controlled trial was undertaken in 457 acute-stroke patients with an average age of 76 years (48 percent women) randomly assigned to stroke unit, general wards with stroke team support, or "domiciliary care", within 72 hours of stroke onset. Outcome was assessed at three, six, and 12 months. The primary outcome measure was death or institutionalization at 12 months. Mortality or institutionalization at one-year were lower in patients on a stroke unit (14 percent) than for those receiving care from a stroke team (30 percent) or "domiciliary care" (24 percent). The proportion of patients alive without severe disability at one-year was also significantly higher on the stroke unit (85 percent) compared with stroke team (66 percent) or "domiciliary care" (71 percent). The authors concluded stroke units are more effective than a specialist stroke team or specialist "domiciliary care" in reducing mortality, institutionalization and dependence after stroke.

Reeder B et al. The Saskatchewan Clinical Stroke Prevention Project: design; *Health Rep* 1994;6(1):139-41.

This article discusses plans for interventions among family physicians to increase the use of stroke prevention strategies. These interventions include seminars, printed educational material, one-on-one case discussions, academic detailing, self-documented chart audit and system changes. No outcome data is available yet from this study.

Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation: does efficacy in clinical trials translate into effectiveness in practice? Harvard Community Health Plan, Brookline, MA. *Arch Int Med* Sep 1994;154(17):1945-53.

A study from the Harvard Community Health Plan to determine whether recommendations from clinical trials had been implemented into routine practice. The study also attempted to determine if the low complication rates achieved in clinical trials were matched in community practice. Seventy-nine percent of eligible patients were on warfarin. Target INRs were achieved in 50 percent of patients on warfarin. The incidence of stroke and major or minor hemorrhage was slightly above those found in the clinical trials.

Indredavik B et al. Stroke unit treatment. Long-term effects. *Stroke* Oct 1997;28(10):1861-66.

The aim of this randomized controlled trial was to examine the long-term effects of the stroke unit care. A total of 110 patients with symptoms and signs of an acute stroke were allocated to the stroke unit and 110 patients were allocated to general wards. After five years, 38 (34.5 percent) of the patients randomized to the stroke unit and 20 (18.2 percent) of the patients randomized to the general wards were at home. Sixty-five (59.1 percent)

of the patients from the stroke unit and 78 (70.9 percent) of the patients from the general wards died, while seven (6.4 percent) and 12 (10.9 percent), respectively, were in an institution (e.g., nursing home). The functional state of the patients was significantly better for those who were treated in the stroke unit. This study shows that stroke unit care improves long-term survival and functional state and increases the proportion of patients able to live at home five years after the stroke. Combined acute and rehabilitation stroke units appear to be an effective way of organizing treatment for acute stroke patients.

Indredavik B et al. Stroke unit treatment improves long-term quality of life: a randomized controlled trial. *Stroke* May 1998;29(5):895-99.

In a randomized controlled trial, 110 patients with signs and symptoms of an acute stroke were allocated to the stroke unit and 110 to general wards. The primary aim of the present trial was to examine whether treatment in a stroke unit had an effect on different aspects of quality of life for stroke patients up to five years after the onset of stroke. After five years, the quality of life appeared to be significantly better in the stroke unit than in the general wards group. Patients who were independent in activities of daily living had significantly better quality of life assessed by the Nottingham Health Profile and Frenchay Activities Index scales (addressed in the article) than patients who were dependent. Significant differences in favor of the stroke unit were present for the dimensions of energy, emotional reactions, social isolation, physical mobility and sleep, although no difference was noted for the category of pain. This study shows that stroke unit care improves different aspects of long-term quality of life for stroke patients.

Ronning OM, Guldvog B. Stroke units versus general medical wards, 1: twelve- and eighteen-month survival: a randomized, controlled trial. *Stroke* Jan 1998;29(1):58-62.

The hypothesis that a stroke unit with short length of stay increases one-year and 18-month survival rates was tested in this study. A quasi-randomized, controlled study was undertaken among 802 patients ≥ 60 years of age admitted to the hospital in Norway with a diagnosis of stroke between January 1, 1993, and February 1, 1995. All patients with onset of symptoms < 24 hours before admittance were enrolled (802), followed until death or to the end of the observation period (18 months) and were allocated to a stroke unit or a general medical ward. Fatality within the first ten days was 8.2 percent among patients in the stroke unit and 15.1 percent among patients in the general medical ward. One-year survival among patients treated in the stroke unit was 70.6 percent and in the general medical wards 64.6 percent; 18-month survival rates were 65.1 percent and 58.0 percent respectively. Stroke units increase survival rates among stroke patients compared with general medical wards. The effect on survival occurs early after the stroke and sustains during at least 18 months of observation.

Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ* Apr 19, 1997;314(7088):1151-59.

The objectives of this review was to define the characteristics and determine the effectiveness of organized inpatient (stroke unit) care compared with conventional care in reducing death, dependency, and the requirement for long term institutional care after stroke. A systematic review of all randomized trials that compared organized inpatient stroke care with the contemporary conventional care was conducted. Specialist stroke unit interventions were defined as either a ward or team exclusively managing stroke (dedicated stroke unit) or a ward or team specializing in the management of disabling illnesses, which include stroke. A total of 12 trials randomized a total of 2,060 patients to a dedicated stroke unit or a general medical ward, six trials (647 patients) compared a mixed assessment/rehabilitation unit with a general medical ward and four trials (542 patients) compared a dedicated stroke unit with a mixed assessment/rehabilitation unit. Stroke unit care was associated with a long term (median one year follow-up) reduction of death, dependency or the need for institutionalization. These observed benefits were not restricted to any particular subgroup of patients or model of stroke unit care.

Stroke Unit Trialists Collaboration. How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. *Stroke* Nov 1997;28(11):2139-44.

A collaborative systematic review of all randomized trials (19) that compared organized inpatient (stroke unit) care with contemporary conventional care was performed. Of these 19 trials, 18 (3,246 patients) could provide outcome data on death, place of residence and final functional outcome. The reduction in case fatality of patients managed in a stroke unit setting developed between one and four weeks after the index stroke. The reduction in the odds of death was evident across all causes of death and most marked for those deaths considered to be secondary to immobility. The relative increase in the number of patients discharged home from stroke units as opposed to conventional care was largely attributable to an increase in the number of patients returning home physically independent. Within the limitations of the available data, the authors concluded that organized inpatient stroke unit care probably benefits a wide range of stroke patients in a variety of different ways, (i.e., reducing death from secondary complications of stroke and reducing the need for institutional care through a reduction in disability).

Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2000;(2):CD000197.

The objective of this review was to assess the effect of care in a stroke unit compared with the conventional care of patients following a stroke. Randomized and quasi-randomized trials comparing organized inpatient stroke unit care with conventional care were reviewed. Twenty trials were included. Stroke unit care showed a reduction in the odds of death

recorded at final follow-up. The odds of death or institutionalized care were lower, as were death or dependency at final review. Subgroup analyses showed that the observed benefits were independent of patient age, sex, stroke severity, and types of stroke unit organization. There was no indication that organized stroke unit care resulted in increased hospital stay, although there was heterogeneity between the trials. Stroke patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke. The apparent benefits are not restricted to any particular sub-group of patients or model of stroke unit care. No systematic increase was observed in the length of inpatient stay.

Webb DJ et al. Effects of a specialized team on stroke care. The first two years of the Yale Stroke Program. *Stroke* 1995 Aug;26(8):1353-57.

In an effort to document the effects of a new program of specialized stroke care, patients discharged with a stroke diagnosis (diagnosis-related group 14) over a six-year period between January 1987 and December 1992 were evaluated. Stroke team involvement was associated with a shortened median length of stay from 10 to 8 days. After stroke team involvement, there were fewer urinary tract infections, and those patients who developed infection had a shorter length of stay. There was no change in the rate of aspiration pneumonia or in the length of stay for patients with aspiration pneumonia. Mortality did not change. A coordinated, multidisciplinary approach to stroke care may reduce length of stay and morbidity in patients hospitalized because of stroke.

Wee AS et al. The development of a stroke clinical pathway: an experience in a medium-sized community hospital. *J Miss State Med Assoc* Jul 2000;41(7):648-53.

Patients with acute ischemic strokes discharged between January 1, 1994 and December 31, 1994 were studied in a medium-sized community hospital in Mississippi. The medical records were reviewed for: 1) if a brain CT scan was performed and the timing of the procedure; 2) whether the patient received any emergent treatment for hypertension; 3) the search for an etiology of the cerebral infarct; 4) preventive measures against DVT; and, 5) preventive drug therapy for stroke at the time of discharge. A clinical pathway was then implemented which emphasized the five indicators above. Following the clinical pathway implementation, a follow-up study was performed which showed significant improvement. In the baseline study among those patients who had a CT scan, 76 percent were performed within 24 hours and 22 percent of patients received emergent treatment for hypertension (94 percent of these patients received sublingual nifedipine). In the follow-up study, 95 percent CT scans were performed within 24 hours, no patients were treated emergently for hypertension, a significant increase in the use of prophylactic measures to prevent DVT and also an increase in antithrombotic medication prescription at discharge was noted. When applied properly, clinical pathways can effectively mobilize hospital resources, maximize quality of care, and at the same time minimize costs.

Miscellaneous

Albers GW. Choice of endpoints in antiplatelet trials: which outcomes are most relevant to stroke patients? *Neurology* Mar 14, 2000;54(5):1022-28.

In addition to ASA, three other antiplatelet agents (ticlopidine, clopidogrel and ASA plus extended-release dipyridamole) have been shown to be effective in preventing stroke in patients with cerebrovascular disease. The absence of direct comparisons and differences in the study designs, data analysis techniques and patient populations evaluated with these agents makes determination of their relative efficacies difficult. The variability in the choice of primary endpoints for individual trials contributes substantially to the controversy regarding the efficacy of antiplatelet agents. The choice of endpoint has a considerable impact on the outcome and interpretation of clinical trials, yet there continues to be no consensus. The benefit of antiplatelet therapies for patients with recent cerebrovascular events is determined most accurately if stroke alone is chosen as the primary endpoint.

American Heart Association. 1999 *Heart and Stroke Statistical Update* 1999.

This update is based on 1996 data in the areas of stroke and other cardiovascular diseases. Information categories include mortality, risk factors, medical procedures, facilities and costs.

Goldstein LB, et al. US national survey of physician practices for the secondary and tertiary prevention of ischemic stroke: design, service availability and common practices. *Stroke* Sept 1995;26(9):1607-15.

This was a survey of physicians asking about the availability of diagnostic facilities for stroke in their practice venue. Over 90 percent of physicians had carotid ultrasonography, transthoracic echocardiography, Holter monitoring and brain imaging by CT scan and MRI available to them. MR angiography was available to 68 percent and transesophageal echocardiography to 74 percent. There were wide geographic variations in the availability of CEA. A majority of physicians reported using warfarin and antiplatelet drugs in appropriate patients.

Gubitz G, Phillips S and Aguilar E. Discharge disposition of patients on an acute stroke unit. *J Stroke and Cerebrovasc Dis* Sept-Oct 1999;8(5):330-35.

This purpose of this Canadian study was to determine which patients admitted to an acute stroke unit experienced a delay in their discharge, the reasons for delays and the costs accrued. Age, gender, stroke type, length of stay, discharge disposition and cause of discharge delay were reviewed for all patients with TIA, cerebral infarction and intracerebral hemorrhage admitted to the acute stroke unit between January 1, 1994 and December 31, 1996. Of the 729 patients admitted, 75 percent had a cerebral infarction, 15 percent had a TIA and 10 percent had an intracerebral hemorrhage. Discharge was delayed in 29 percent of the patients. Patients with TIA were least likely to experience a delay. For

patients who were ultimately sent home 37 percent of delays were attributed to waiting for test results and physician consultations. The greatest cause of delay for those patients waiting for discharge was the lack of an available bed at a rehabilitation facility or nursing home, which accounted for 78 percent of the non-medical bed days and cost \$1.16 million (Canadian).

Hart CL et al. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrow/Paisley study in Scotland. *Stroke* Aug 2000;31(8):1893-96.

The aim of this study was to relate risk factors in middle-aged men and women to stroke incidence (defined by having a hospital discharge with a main diagnosis of stroke) and compare this with the associations between risk factors and stroke mortality. In the early to mid-1970s, when they were 45 to 64 years of age, 7,052 men and 8,354 women from the Renfrow/Paisley prospective cohort study in Scotland were screened. Measured risk factors included blood pressure, blood cholesterol and glucose, respiratory function, cardiothoracic ratio, smoking habit, height, body mass index, preexisting coronary heart disease (CHD) and diabetes. These factors were related to stroke incidence over 20 years of follow-up. Diastolic and systolic blood pressure, smoking, cardiothoracic ratio, preexisting CHD, and diabetes were positively related to stroke incidence for men and women, whereas adjusted forced expiratory volume and height were negatively related. Former smokers had similar stroke rates to never-smokers. The risk factors had a similar effect on stroke incidence as on stroke mortality. Epidemiological studies with information on stroke mortality are likely to give results applicable to stroke incidence.

Holroyd-Leduc JM et al. Sex differences and similarities in the management and outcome of stroke patients. *Stroke* Aug 2000;31(8):1833-37.

Little data exist on whether gender differences exist in stroke patients. This study was conducted to determine whether gender differences exist in patients with acute stroke admitted to Ontario hospitals. Using linked administrative databases, a population-based cohort study was performed. The databases contained information on all 44,832 patients discharged from acute-care hospitals in Ontario between April 1993 and March 1996 with a diagnosis of acute stroke. Male stroke patients were more likely than female stroke patients to have a history of ischemic heart disease (18.1 percent versus 15.3 percent) and diabetes mellitus (20.1 percent versus 18.7 percent). Female patients were more likely than male patients to have hypertension (33.8 percent versus 30.0 percent) and AF (12.9 percent versus 10.2 percent). Among stroke survivors ≥ 85 years, men were more likely than women to receive aspirin (36.0 percent versus 30.7 percent) and ticlopidine (9.2 percent versus 6.8 percent). The use of warfarin was similar for the two genders. The risk of death one-year after stroke was somewhat lower in women than men (95 percent).

Karatas M et al. Functional outcome in stroke patients with atrial fibrillation. *Arch Phys Med Rehabil* Aug 2000;81(8):1025-29.

This retrospective case-comparison study was designed to identify the prevalence of AF in a sample of stroke patients and to evaluate the impact of AF on patient clinical characteristics and functional outcome. A total of 196 of 231 consecutive stroke patients admitted to inpatient rehabilitation units were evaluated during the rehabilitation period. AF was diagnosed in 41 (20.1 percent) patients. Patients who had AF were more likely to have ischemic cerebral lesions. There were no significant differences between the AF and non-AF groups with regard to mean age, length of stay and disease duration. AF is not only associated with increased risk of stroke, but also with markedly greater disability in stroke patients. Factors such as size and type of cerebral lesions, stroke severity, comorbid conditions and impact of AF on systemic and cerebral circulation can influence stroke recovery.

Kammersgaard LP et al. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: a case-control study: the Copenhagen stroke study. *Stroke* Sep 2000;31(9):2251-6.

In this case-control study, the feasibility and safety of inducing modest hypothermia by a surface cooling method in awake patients with acute stroke was evaluated. A total of 17 patients with stroke admitted within 12 hours from stroke onset were prospectively included. Patients were kept awake and given hypothermic treatment for six hours by the "forced air" method, a surface cooling method that used a cooling blanket with a flow of cool air in combination with pethidine to treat shivering. Body temperature decreased from 36.8 degrees Celsius to 35.5 degrees Celsius. Mortality at six months after stroke was 12 percent in cases exposed to hypothermia versus 23 percent in controls. A large, randomized clinical trial to test the possible beneficial effect of induced modest hypothermia in unselected patients with stroke is needed.

Metropolitan Life Insurance Company, *Statistical Bulletin* Oct.-Dec. 1997.

Data for Americans 40 years old and older for 1995 showed the average in-hospital and physician costs were \$11,010 for a stroke, citing a high of \$17,590 and a low of \$6,670. In-hospital and physician costs for TIA averaged \$4,940 in 1995, with a high of \$6,160 and a low of \$3,170. Length of stay data for the same timeframe ranged from 5.2 days to 8.1 days for stroke and 2.3 days to 5.4 days for TIA.

Oberg AL et al. Incidence of stroke and season of the year: evidence of an association. *Am J Epidemiol* Sept 15, 2000;152(6):558-64.

The objective of this study was to ascertain whether an association exists between the season of the year and the incidence of stroke by using a methodological approach. A longitudinal study design was used involving 72,779 veterans hospitalized for stroke at any Veterans Affairs hospital nationally during the years 1986-1995. There was clear evidence of a seasonal occurrence for stroke in general. This seasonal effect was found

for ischemic stroke, but not for hemorrhagic stroke. The peak occurrence was in mid-May. Neither the region (i.e., climate) nor the race of the patient substantially modified the seasonal trend. An explanation for this pattern remains to be determined.

Post-Stroke Rehabilitation: Clinical Guideline Number 16; Agency for Health Care Policy and Research Publication May 1995;# 95-0062.

This patient education tool is designed for distribution to the patient and their family. It includes information regarding recovery, residual effects, acute care treatment, stroke prevention and rehabilitation. Additional resources are also referenced.

Samsa GP et al. Epidemiology of recurrent cerebral infarction. A Medicare claims-based comparison of first and recurrent stroke on 2-year survival and cost. *Stroke* Feb 1999;30(2):338-49.

Using a random 20 percent sample of Medicare patients aged 65 years and older admitted with a primary diagnosis of cerebral infarction during calendar year 1991, the authors used historical data from the previous four years to classify patients as having either first or recurrent stroke, then followed survival and direct medical costs for 24 months after stroke. Survival from first stroke is consistently better than that for recurrent stroke: 24-month survival was 56.7 percent versus 48.3 percent, respectively. Costs were similar for the initial hospital stay and in the first three months after stroke. However, during months four to 24 after stroke, total costs were higher among those with recurrent stroke by approximately \$375 per month across all patients, with this difference being greatest for younger patients and least for patients aged 80 years or older. Patients with recurrent stroke have, on average, poorer outcomes than those with first stroke. To be as accurate as possible, clinical policy analyses should use different estimates of health and cost outcomes for first and recurrent stroke.

Possible Emerging Therapy

Mayberg MR and Furlan A. Ancrod Is Snake Venom an Antidote for Stroke? *JAMA* May 10, 2000;283(18):2440-42.

This editorial comments on the STAT study by Sherman and colleagues. Because STAT essentially used a three-hour window (only 82 patients were treated after three hours), this study begs the question of whether ancrod is "better" than tPA. The 8 percent absolute benefit in essentially full neurologic recovery with ancrod is somewhat less impressive than the 12 percent benefit reported with intravenous tPA, although the outcomes for these drugs cannot be compared directly without a head-to-head trial. Despite these findings, the editorial authors disagree with the assertion that ancrod may be safer than thrombolytic agents for the treatment of acute ischemic stroke. The 5 percent rate of symptomatic brain hemorrhage with ancrod is similar to the 6 percent rate with intravenous tPA. Perhaps the most compelling observations from the study by

Sherman et al relate to the concordance between early reduction in serum fibrinogen levels in ancrod-treated patients and subsequent functional outcome. For patients receiving ancrod, there was a notable improvement in primary outcome (45.8 percent versus 34.6 percent) when the six-hour serum fibrinogen levels were therapeutic, without an apparent increased incidence of hemorrhage. This supports the role of fibrinogen in the pathophysiology of stroke and suggests that the efficacy of ancrod might be further improved by early monitoring and intervention in the dosing regimen.

Orbach D and Levine D. Outcomes of ancrod in acute ischemic stroke. *JAMA* Oct 18, 2000;284(15):1926-27.

In this letter to the editor, the authors note the patients in the placebo group who presented before three hours had elapsed from the onset of stroke symptoms fared better than patients presenting later, whether given placebo or ancrod. One possible interpretation is that the time lag between symptom onset and presentation to the hospital is actually an indirect marker for stroke severity. This possibility is important because, if true, it would confound the interpretation of studies of acute stroke treatment. The authors indicate their hope that the work of studying the time to presentation will be undertaken and published in the near future.

In response to the above letter highlighting the worse outcomes of patients who received placebo with increasing time to treatment, Dr. Sherman indicated this observation also struck the STAT study authors. The STAT data results verify that those who received placebo and entered the STAT study later after stroke onset had worse stroke severity than those entering earlier. While the number of patients enrolled at less than two hours and more than three hours is relatively small, the impact of stroke severity on outcome is profound and, as suggested by Orbach and Levine, this probably explains the observed worsening outcome.

Dr. Sherman addresses two additional points which deserve brief attention: 1) as the NINDS trial strictly adhered to a three-hour time limit, the implicit criticism that the NINDS team failed to stratify patients within six hours of stroke onset seems unwarranted. More importantly, the STAT study has no data that permits a detailed exploration into reasons for the change in stroke severity with increasing time to presentation.

Orgogozo JM et al. Outcomes of ancrod in acute ischemic stroke. *JAMA* Oct 18, 2000;284(15):1926-27.

In this letter to the editor, the authors seek to clarify a reference to the European Stroke Treatment with Ancrod Trial (ESTAT) in the article entitled "Intravenous Ancrod for Treatment of Acute Ischemic Stroke." The ESTAT was an ongoing European trial with ancrod administered six hours after stroke onset. The ESTAT Independent Data and Safety Monitoring Board used a group-sequential design to compare overall mortality (not only 90-day mortality) between the ancrod and placebo

treatment groups and at no stage was the boundary of safety crossed. While there was a difference in the 90-day mortality in the patients included in the interim analysis, this is not true of total mortality in the sample. The sequential monitoring included 1,221 patients at the time of study discontinuation, and there was never a statistically significant excess mortality rate in the ancrod group. The analysis of the full data set from ESTAT has not been released, including the follow-up data from all patients enrolled, which may help to gain a clear understanding of the possible benefits and hazards of ancrod in acute ischemic stroke. Any conclusions in advance of such an analysis would be inappropriate. Premature speculation on an increased death rate in ESTAT will only cast doubts on the validity of the positive STAT results and prejudice the potential therapeutic usefulness of ancrod in this setting. A possible explanation for the failure of ESTAT to show a benefit of ancrod as opposed to STAT is the longer time window.

Qureshi AI et al. Intra-arterial recombinant tissue plasminogen activator for ischemic stroke: an accelerating dosing regimen. *Neurosurgery* Aug 2000;47(3):473-76.

Recently attention has been focused on rt-PA for intra-arterial administration. Data are limited regarding the intra-arterial dose, efficacy, and safety profile of this agent. The authors prospectively studied eight consecutive patients with acute ischemic stroke who were referred for intra-arterial thrombolysis. Each patient was considered to be a poor candidate for intravenous therapy by the treating neurologist. A maximum total dose of 40 mg of r-tPA was administered intra-arterially. Angiograms were obtained after each 10 milligrams of r-tPA, and responses were graded. Intervals from presentation to treatment initiation ranged from one to eight hours. After administration of r-tPA, neurological improvement was observed in four patients. Asymptomatic intraparenchymal hemorrhage was observed on CT scan in two patients at 24 hours. This study suggests that intra-arterial r-tPA in doses up to 40 milligrams is relatively safe. The dose appears to facilitate the recanalization process by lysis of local thrombus and improvement in distal flow.

Sherman DG et al. Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. *Stroke Treatment with Ancrod Trial JAMA* May 10, 2000;282(18):2395-403.

The Stroke Treatment with Ancrod Trial (STAT), a randomized, parallel-group, double-blind, placebo-controlled trial was conducted between August 1993 and January 1998 in 48 centers to evaluate the efficacy and safety of the defibrinogenating agent ancrod in patients with acute ischemic stroke. Patients were randomly assigned to receive ancrod (n=248) or placebo (n=252) as a continuous 72-hour intravenous infusion beginning within 3 hours of stroke onset, followed by infusions lasting approximately 1 hour at 96 and 120 hours. Favorable functional status (defined as a need for little or no help in daily activities) was achieved by more patients in the ancrod group (42.2 percent) than in the

placebo group (34.4 percent). Mortality was not different between treatment groups and the proportion of severely disabled patients was less in the ancrod group than in the placebo group (11.8 percent versus 19.8 percent). The favorable functional status observed with ancrod versus placebo was consistent in all subgroups defined for age, stroke severity, sex, prestroke disability, and time to treatment ≤ 3 or > 3 hours after stroke onset). There was a trend toward more symptomatic intracranial hemorrhages in the ancrod group versus placebo (5.2 percent versus 2.0 percent), as well as a significant increase in asymptomatic intracranial hemorrhages (19.0 percent versus 10.7 percent). In this study, ancrod had a favorable benefit-risk profile for patients with acute ischemic stroke.